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Report

Cancer incidence in multiple sclerosis and effects of immunomodulatory treatments

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Summary

Multiple sclerosis (MS) has been linked to reduced rates of cancer prior to the era of immunomodulating treatments. We assessed the incidence of cancer in a cohort of 1338 MS patients and evaluated the effect of exposure to immunomodulatory treatment. Cancer incidence in the MS population was compared with the expected age- and gender-matched incidence rates in the Israeli population for the period 1960–2003. Time-dependant Cox model analysis was used to estimate hazard ratios for glatiramer acetate, β-interferons (1a and 1-b) and intravenous immunoglobulins (IVIg). Among 892 female MS patients, 15 (1.7%) developed breast cancer, and 31 (3.5%) developed cancers of any type. Seventeen of 446 (3.8%) male MS patients developed cancer. The standardized incidence ratios (SIRs) computed until the time of first immunomodulatory treatment were 0.60 (95% CI, 0.38–0.92, $p = 0.02$) for all female cancer, and 1.11 (95% CI, 0.64–1.91) for all male cancer. Time-dependent covariate analyses for female breast cancer yielded a relative risk for glatiramer acetate of 3.10 (95% CI, 0.86–11.1) and 0.52 (95% CI, 0.07–4.05) for β-interferons. For IVIg, the analyses were uninformative. Our findings indicate that cancer incidence is significantly lower in female MS patients than in the general population. Female MS patients treated with glatiramer acetate showed an elevated rate of breast cancer and all MS patients treated with β-interferons showed an elevated risk of non-breast cancers though not statistically significant ($p = 0.122$ and 0.072, respectively). Further study is needed to assess possible associations between long-term exposure to the novel immunomodulatory treatments in MS and rate of caner.

Introduction

Autoimmunity develops when the immune system is activated against 'self' antigens and results in a disease state. Autoreactive T cells directed against cryptic self-determinants are part of the normal immune repertoire and can be involved either in prevention or promotion of immunopathology and cancer [1]. The association between cancer and autoimmune diseases is not yet fully elucidated [2,3]. On the one hand, studies have indicated increased relative risk (RR) for cancer in patients with systemic lupus erythematosus (RR 1.3), rheumatoid arthritis (RR 1.07) and systemic sclerosis (RR 1.5), with more pronounced elevations for the lymphoproliferative cancers [4–13]. The long-term exposure of patients suffering from these disorders to immunosuppressive therapy may have confounded the association with cancer. On the other hand, it has been suggested that the autoimmune 'haplotype' [14] protects against infections and malignancy. MS is a putative autoimmune disease affecting the central white matter and results in progressive neurological disability over time. The onset of the disease is usually between 20 and 40 years of age, with a peak incidence at 25 years, and the disease is more common in females [15]. The pathogenic mechanisms involved in MS are associated with autoimmune response of autoreactive T cells against myelin peptides. As MS is a chronic autoimmune disease, the immunogenic process that leads to persistent immune stimulation [16], may inhibit carcinogenesis. Despite the fact that MS is one of the more frequently studied autoimmune diseases of the central nervous system, there are only few studies reporting the incidence of cancer in MS [17–24]. We hypothesized that the risk to develop cancer might be reduced in patients with MS, compared to age- and gender-matched general population rates. On the other hand, the recent use of the new immunomodulatory drugs [i.e., β-interferons, glatiramer acetate, and intravenous IgG immunoglobulins (IVIg)] for the treatment of MS may abolish this presumed protection or even increase the incidence of cancer in these young patients. Since treatment with immunomodulatory drugs is frequently given shortly after diagnosis and patients will receive these treatments for long periods [25], it is of utmost importance to evaluate the frequency of cancer in both treated and untreated MS patients.

In the present study we linked data from the National Cancer Registry of Israel to the computerized database at the Multiple Sclerosis Center, Sheba Medical Center, Tel-Hashomer, Israel. We compared cancer incidence rates in a large cohort of MS patients with rates in the Jewish population of Israel. Analyses were also carried out for the period before and after exposure to immunomodulatory (non-cytotoxic) treatments to determine whether patients treated by β-interferons, glatiramer acetate, or IVIg were at increased risk of cancer.

Methods

Subjects

All patients with MS according to Poser criteria [26] followed at the Multiple Sclerosis Center, Sheba Medical Center, Tel-Hashomer, Israel, were included in the present analysis. All patients' records in the MS computerized database were meshed with records of the Israeli National Cancer Registry within the Israeli Center for Disease Control (ICDC) to identify pathologically confirmed cancer co-morbidity.

The reporting of cancer cases is compulsory in Israel, and all cancer patients are supposed to have been reported to the ICDC since 1960.

We thus identified all MS patients with pathologically confirmed cancers (according to the International Classification of Diseases, 9th Revision, CM), diagnosed through December 31, 2003. Information was available on patient age, gender, ethnicity, age at MS onset, age at cancer onset and type of cancer, if any, age at end of follow-up on 12-31-03 and ages at exposure to the various immunomodulatory treatments. These treatments included glatiramer acetate, β-interferons (interferon-β-1a, and interferon-β-1b) and IVIg. Thirty four patients who received cytotoxic treatments (immuran, linomide, methotrexate or cytoxan) were excluded from the analysis, as was one patient with missing covariate information. Family history and BRCA1 and BRCA2 mutations were assessed for patients with breast cancer. The Israeli Ministry of Health Ethical Committee approved the study.

Statistical analysis

To compare cancer incidence rates in MS patients with the general population, standardized incidence ratios (SIR) were based on the Jewish population of Israel. In first analysis, patients were at risk until the earliest of first use of immunomodulatory therapy, cancer onset, death or end of follow-up on 12-31-03. In the second analysis, patients remained at risk until the earliest of cancer, death or the end of follow-up on 12-31-03. In the third analysis, patients were at risk from the first use of immunomodulatory therapy to the earliest of cancer, death or the end of follow-up on 12-31-03.

To examine whether MS patients who received immunomodulatory treatments were at increased risk of cancer, we used a time-dependent covariate (TDC) in a gender-stratified Cox model as an indicator of whether a treatment had been taken up to a given age [27]. This technique amounts to a case-control analysis comparing the history of immunomodulatory therapy use in MS patients who develop cancer at a given age with age-matched controls, namely all who have not yet developed cancer by that age. At the age of cancer incidence, the patient's treatment status (TDC) was compared with the TDC of others of the same age and gender who had not previously developed cancer. For a given gender, the case and those that the case is compared with are called the 'risk set' at the age t, of the case's cancer incidence. To be in the risk set at age t, a subject needed to be alive at age t and to have attained age t at or before the date of the end of study follow-up. In addition, the subject must have had a diagnosis of MS before age t and not have developed the cancer before age t. To study the effects of treatments, we used the following time-dependent covariates: $z_1(t) = 1$ if the person took glatiramer acetate between his or her ages of MS onset and age t and 0 otherwise; $z_2(t) = 1$ if the person took IVIg between his or her ages of MS onset and age t and 0 otherwise; and $z_3(t) = 1$ if the person took β-interferons between his or her ages of MS onset and age t and 0 otherwise. Two-sided tests of significance for these time-dependent covariates were based on the likelihood ratio statistic from the Cox partial likelihood [28], and the 0.05 level was used to determine statistical significance.

Results

Of the 1338 MS patients' records analyzed, 892 (67%) were female and 433 (33%) male. Fifty-five percent were Ashkenazi, 34% Sephardic, and the rest of mixed origin. This ethnic composition is similar to that of the general Israeli population, which includes 62% Ashkenazi, 29% Sephardic, and 9% of other ethnic groups [29]. The majority of patients (58%) had a relapsing-remitting disease course, 21% a secondary progressive course, 8% a primary progressive course, and 13% a diagnosis of probable MS.

Among 892 female MS patients, 15 (1.7%) developed breast cancer, and 31 (3.5%) developed cancers of any type. Seventeen of 446 (3.8%) male MS patients developed cancer. The SIRs computed for patients prior to exposure to treatment were 0.60 [95% confidence interval (CI), 0.38–0.92] with $p = 0.02$ for all female cancer, 0.95 (95% CI, 0.53–1.71) for female breast cancer, and 1.11 (95% CI, 0.64–1.91) for male cancer (Table 1). Thus, female cancer rates, and particularly female non-breast cancer rates, were significantly lower in the MS cohort than in the general population, but no reduction was found in men. Corresponding SIRs

computed until the end of follow-up (including time on immunomodulatory treatment) were 0.71 (95% CI, 0.50–1.00) with $p = 0.054$, 0.97 (95% CI, 0.59–1.62), and 1.11 (95% CI, 0.69–1.79), respectively (Table 1).

Following initiation of immunomodulatory therapy 4 female breast cancers (1, 4, 4 and 7 years of exposure to immunomodulatory therapy), 7 other cancers in women (2, 2, 2, 3, 3, 8 and 11 years of exposure to immunomodulatory therapy), and 4 cancers in men (1, 1, 4 and 9 years of exposure to immunomodulatory therapy), occurred (Table 1). SIRs were all close to 1.0 with wide confidence intervals. Although the evidence is scant, these SIRs raise the possibility that the favorable cancer rates among women with MS before immunomodulatory therapy may have been offset by the effects of treatment.

To examine this question further, we conducted a time-dependent analysis that takes the duration of immunomodulatory therapy into account (Table 2). These analyses for female breast cancer yielded a relative risk for glatiramer acetate ($z_1(t)$) of 3.10 (95% CI, 0.86–11.1), and a relative risk for β-interferons ($z_3(t)$) of 0.52 (95% CI 0.07–4.05), but these associations were not statistically significant. Data for IVIg were too sparse to be informative (Table 2). Relative risks for non-breast cancers in an additional analysis stratified by gender (Table 2) were 1.77 (0.62–5.12) for glatiramer acetate ($z_1(t)$), 1.25 (95% CI, 0.38–4.12) for IVIg ($z_2(t)$), and 2.23 (95% CI, 0.99–5.01) for β-interferons ($z_3(t)$). None of these results was statistically significant. The significance levels in Table 2 are not adjusted for multiple comparisons, as several cancer outcomes (breast cancer versus non-breast cancer) and various immunomodulatory treatments were examined. Some patients were given more than one immunomodulatory treatment, but because of the sparsity of the data, we could not investigate joint effects of various treatments.

Only two MS patients with breast cancer had familial history of cancer. Founder mutations in BRCA1 or

Table 1. Standardized Incidence Ratios (SIRs) compared to Jewish Israeli population

	Observed	Expected	SIR	95% CI	*p*
Before initiation of immunomodulatory treatment[a]					
Female breast cancer	11	11.6	0.95	0.53–1.71	0.86
All female cancer	20	33.59	0.60	0.38–0.92	0.02
All male cancer	13	11.74	1.11	0.64–1.91	0.71
From initiation of immunomodulatory treatment to end of follow-up on 12-31-01[b]					
Female breast cancer	4	3.8	1.05	0.39–2.80	0.92
All female cancer	11	10.23	1.08	0.60–1.94	0.81
All male cancer	4	3.54	1.13	0.42–3.01	0.81
To end of follow-up on 12-31-01[c]					
Female breast cancer	15	15.40	0.97	0.59–1.62	0.92
All female cancer	31	43.82	0.71	0.50–1.00	0.054
All male cancer	17	15.28	1.11	0.69–1.79	0.66

[a] Patient is at risk until the earlier of initiation of immunomodulatory treatment, cancer incidence, death, or 12-31-03.
[b] Patient is at risk from initiation of any immunomodulatory treatment to the earlier of cancer incidence, death or 12-31-03.
[c] Patient is at risk until the earlier of cancer incidence, death or 12-31-03.

Table 2. Effects of treatments on female breast cancer risk and on all non-breast cancer risk

	Hazard ratio	95% CI	χ^2	*p*
Effect on female breast cancer				
Glatiramer acetate (Z_1)	3.10	0.86–11.1	2.39	0.122
IVIg (Z_2)	0.00	0–∞	2.62	0.106
β-Interferons (Z_3)	0.52	0.07–4.05	0.47	0.495
Effect on non-breast cancers				
Glatiramer acetate (Z_1)	1.77	0.62–5.12	0.99	0.321
IVIg (Z_2)	1.25	0.38–4.12	0.13	0.721
β-Interferons (Z_3)	2.23	0.99–5.01	3.25	0.072

*Analyses stratified by gender.
Female breast cancer = 4 cases after any immunomodulatory therapy.
All non-breast cancer = 7 female cases and 4 male cases after any immunomodulatory therapy.
Degree of freedom (DF) was 1 for all rows.

Table 3. Summary of cancer related epidemiological studies in multiple sclerosis

Author/year	MS sample size	Geographic location	Index period	Observed/expected cancer cases	Prevalence SIR/SMR/RR	Design	Authors' comments
Percy et al. [23]	67	Minnesota, USA	1905–1964	6/not defined	Not reported	Retrospective cohort	Rate of neoplasms does not differ from those expected in the general population of the community
Palo et al. [22]	2206	Finland	1961–1974	15/15.9	Prevalence = 0.64 vs. 0.72, $p < 0.005$.	Retrospective cohort compared to cancer registry	Low prevalence and mortality rates of cancer among MS patients
Allen et al. [17]	120	Ireland	1929–1977	19/33[a]	Not reported	Nacropsy-proven cases compared to matched neurological and general controls	Incidence of malignancy is not significantly different from the general population
Sadovnick et al. [19]	3126	Vancover & Ontario, Canada	1972–1988	19/24[a]	SMR = 0.67, $p < 0.01$	Retrospective cohort of causes of death compared to Ministry of Health Registry	The proportion of deaths due to malignancy was the same for MS patients and the age-matched general population
Moller et al. [21]	5359	Denmark	1971–1987	210/172	RR = 1.29, p = NS	Retrospective cohort compared to cancer registry	A patient with MS is not at unusual risk for subsequent cancer development
Midgard et al. [20]	1271	Norway	1953–1992	73/84.44	SIR = 0.86	Retrospective cohort compared to cancer registry	MS patients are not at unusual risk for subsequent development of cancer compared to the normal population
Koch-Henriksen et al. [18]	8142	Denmark	1949–1993	524/655[a]	SMR = 0.79	Retrospective cohort compared to national registry of causes of death	MS patients have reduced risk of dying from cancer
Bronnum-Hansen et al. [24]	9881	Denmark	1949–1999	410/4053	SMR = 0.85	Retrospective cohort compared to national registry of causes of death	MS patients have reduced risk of dying from cancer
Achiron et al./ Current study	1338	Israel	1960–2003	Women – 20/33.6 Men – 13/11.7	For women, SIR = 0.60 $p = 0.02$ before treament. For men, SIR = 1.11 $p = 0.71$	Retrospective cohort compared to National Cancer Registry	Pre-treatment risk of cancer is reduced in women with MS. No reduction is seen in men, but confidence intervals are wide.

[a]Autopsy cases; SMR = standardized mortality ratio; SIR = standardized incidence ratio; R = relative risk; NS = non-significant.

BRCA2 were found in four of the 15 women with breast cancer, including one patient with 617delT and three patients with Tyr978X. None were positive for the 5382lnsC or 185delAG mutations. None of the female patients in this subgroup (with either familial or genetic risk) were treated with immunomodulatory drugs.

Discussion

The introduction of long-term immunomodulatory treatments for MS patients has favorably affected disease course and patients' quality of life. However, exposing these relatively young patients to compounds that affect the immune system may confer risks as well as benefits. The present study is the first attempt to analyze possible effects of immunomodulatory non-cytotoxic treatments on the incidence of cancer in MS patients.

Our data suggest that women with MS have reduced cancer incidence compared to the general Israeli population. The reduced incidence of all female cancers held true both before initiation of immunomodulatory treatment ($p = 0.02$, Table 1) and for the entire follow-up period ($p = 0.054$). However, exposure to immunomodulatory treatment resulted in a relative increase of cancer rate, suggesting that these treatments may have offset the protective autoimmune effect. No evidence of reduced cancer risk in male MS patients was found. Thus, the hypothesis that hyperactivation of the immune system protects the body from other insults associated with the development of cancer was supported by our data only for female patients.

The association between cancer and MS has been reported in the literature in eight studies, [17–24] spanning the period between 1905 and 1999 (Table 3). In four of these studies, [17–19,24] the reported outcome was the proportion of deaths due to cancer, but not the incidence of cancer in the MS population studied. Although these studies reported decreased mortality rates from cancer in MS patients, they do not necessarily reflect decreased cancer incidence. The four studies [20–23], that specifically addressed incidence or prevalence of cancer in MS patients before the introduction of immunomodulatory treatments, yielded results consistent with our findings. Cancer rates were either similar to or reduced in comparison with the general population (Table 3). The prevalence of cancer among 2206 MS patients in Finland was 0.64%, which was lower than in the general population (0.72%) [22]. In Denmark, the relative risk for incident cancer among 5359 MS patients was 1.29 (95% CI, 1.2–3.1). However, the authors concluded that patients with MS are not at unusual risk for subsequent cancer development, as more than half of the observed cancers were non-melanoma skin cancers or tumors of the urinary tract, and detection of these cancers was probably accelerated by the rigorous medical work-up of MS patients [21]. In a retrospective cohort study of 1271 Norwegian MS patients [20], the overall cancer incidence was reduced (SIR = 0.86, 95% CI, 0.68–1.09), although a significant excess of breast cancers was observed (SIR = 1.70, 95% CI, 1.05–2.60).

To investigate whether the introduction of immunomodulatory treatments for MS reduced the possible protection against cancer conferred by the disease we examined SIRs of cancer following initiation of immunomodulatory treatments (Table 1) and the impact of treatments (Table 2). Unfortunately, the data for these analyses are sparse and are based on only 11 cancers in women and 4 in men that occurred following initiation of immunomodulatory therapy. None of the associations approached statistical significance. Nonetheless, the SIRs are near unity (Table 1), raising the possibility that immunomodulatory treatments counter the favorable cancer experience seen in women with MS before initiation of immunomodulatory therapy. Likewise, although none of the individual treatments was statistically significantly associated with cancer outcomes (Table 2), these data hint that glatiramer acetate and β-interferons may be associated with increased risk of non-breast cancers (Table 2) and that glatiramer acetate may be associated with increased breast cancer risk (Table 2). It is of interest to note that none of the female patients treated with glatiramer acetate who developed breast cancer had a family history of breast cancer or a founder mutation.

To summarize, our data indicate that women, but not men, with MS are at reduced risk of cancer compared to the general Israeli population before initiation of immunomodulatory therapy. Following initiation of such therapy, the numbers of cancers observed were too sparse to warrant firm conclusions. However, the data raise the possibility that MS patients treated by immunomodulation have cancer rates comparable to that of the general Israeli population. More data are needed to determine whether the positive but not statistically significant associations with use of glatiramer acetate or β-interferons and increased cancer rates represent more than chance findings.

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